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(54) Use of epothilones in the treatment of brain diseases associated with proliferative processes

(57) This invention provides the use of an Epothilone, which shows an average distribution coefficient between plasma and brain of 0.3 to 1.5 in the mouse intravenous bolus injection assay, for the preparation of

a medicament for the treatment of a brain disease associated with proliferative processes.

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Description**Field of the Invention**

5 [0001] The present invention relates to the use of Epothilones in the treatment of brain diseases associated with proliferative processes, especially primary or secondary brain tumors, multiple sclerosis, and Alzheimer's disease.

Background of the Invention

10 [0002] The possibilities of medicamentous treatment of brain diseases are strongly limited by the existence of the so-called blood-brain-barrier (BBB). While the BBB serves as a protective mechanism for preventing exogenous substances to enter the brain tissue, unfortunately, it also prevents the entry of drugs administered by a conventional mode (orally, parenterally, etc.) (A. Maelicke, *Nachr. Chem. Tech. Lab.* 1989, 37, 32-34).

15 [0003] An important class of brain diseases which are difficult to treat with medicaments for the above-cited reason are diseases associated with proliferative processes such as brain tumors, multiple sclerosis, or Alzheimer's disease. Various studies regarding these diseases, especially cancer, have provided some insights into the efficiency of drug targeting to the brain (W. Shapiro, J. Shapiro, *Semin. Oncol.* 1986, 13, 56-69; M. Donelli et al., *Cancer Chemother. Pharmacol.* 1992, 30, 251-260). As a rule of thumb, a drug reaches higher concentrations in the brain the lower its molecular mass and the higher its lipophilicity is (C. Unger et al., *Klin. Wochenschr.* 1985, 63, 565-571). Nevertheless, 20 it has been found in recent years, that for at least some compounds (M. Fromm, *Int. J. Clin. Pharmacol. Ther.* 2000, 38, 69-74) active exclusion mechanisms exist within the BBB, so that drug uptake by brain tissue cannot be simply calculated from physical or chemical data but has to be determined experimentally.

25 [0004] Some experimental methods have been developed to overcome the restrictions of drug uptake by brain tissue caused by the BBB; e.g., direct intrathecal drug application, use of lipid-soluble carriers, or disruption of the BBB by application of high doses of mannitol or other compounds (E. Galanis et al., *Curr. Opin. Neurol.* 2000, 13, 619-625; H. Lahrmann et al., *J. Neurol. Neurochir. Psychiatr.* 2001, 2, 16-20). These methods are, however, associated with considerable disadvantages and/or undesirable side effects. Most of them can be considered to be in an experimental stage, i.e., they cannot be considered as standard therapies.

30 [0005] As a result of the previous work it can be stated that most cytostatic agents (which is the most important class of drugs for the treatment of diseases associated with proliferative processes) do not reach the same concentration in brain liquor as in blood plasma when applied systemically. For example, it has lately been found that maximum liquor concentrations of 20-30% of the plasma concentrations may be reached when using nitrosoureas, which are considered to be the best BBB penetrating type of cytostatic agents (*Therapiekonzepte Onkologie*; Seeger, S., Schütte, J. (Eds.), 3rd edition, Springer, Berlin 1998). Nitrosoureas and a combination of nitrosoureas with procarbazine and vincristine 35 (PCV therapy) are considered to be standard chemotherapeutic agents for the treatment of brain cancer (H. Lahrmann et al., *J. Neurol. Neurochir. Psychiatr.* 2001, 2, 16-20; E. Galanis et al., *Curr. Opin. Neurol.* 2000, 13, 619-625).

40 [0006] Cytostatic agents can be distinguished according to the mechanism of their pharmacological activity. The most important classes of cytostatic compounds are antimetabolites (e.g. fluorouracil, cytarabine, mercaptopurine), antimitotic agents (e.g. colchicine, paclitaxel, podophyllotoxine, Vinca-alkaloids), alkylating agents (e.g. cisplatin, nitrosoureas, nitrogen mustards), antibiotics (e.g. bleomycin), and agents in respect of which the mechanism of their therapeutic effectiveness is not known (e.g. asparaginase).

45 [0007] Although alkylating agents have been found to be useful for cancer treatment, it is an enormous disadvantage of these compounds that their pharmacological mechanism bears a strong carcinogenic potential itself.

50 [0008] In particular nitroso compounds (nitrosoureas and nitroso amines), which were discussed above to be efficient drugs for the treatment of the brain, show these effects: 57 of 60 nitrosoureas (95 %) tested on carcinogenic activity were active (CD Römpf Chemie Lexikon - Version 1.0, Stuttgart/New York: Georg Thieme Verlag 1995). It would thus be desirable to provide compounds for the efficient treatment of brain diseases associated with proliferative processes which have similar or better BBB-penetrating properties as nitrosoureas, but without their carcinogenic potential.

55 [0009] Within the group of antimitotic agents, Paclitaxel (Taxol®) is the best-known member and one of the best-selling anticancer medicaments in the present time. Unfortunately, paclitaxel has only low ability to penetrate the BBB (M. Glantz et al., *J. Natl. Cancer Inst.* 1995, 87, 1077-1081) and is thus not considered to be useful for the treatment of brain diseases via conventional administration routes. Other antimitotic agents, which block the mitotic spindle of a proliferating cell by binding to the spindle-peptide tubulin, and thus cause apoptosis, have been found to be powerful anticancer agents (K.-H. Altmann, *Curr. Opin. Chem. Biol.* 2001, 5, 424-431), in respect of which less carcinogenic side effects have been reported than in the case of the alkylating agents discussed above. Epothilones also belong to this group of drugs.

60 [0010] The natural products Epothilone A and B as well as some of their synthetic derivatives have recently found interest in connection with the treatment of cancer, and a lot of work has been done on their synthesis (K. Nicolaou et

al., *Angew. Chem.* 1998, 110, 2120-2153) and the synthesis of modified structures.

[0011] WO 99/07692, WO 99/02514 and WO 99/67252 disclose Epothilone derivatives, their synthesis and pharmaceutical use.

[0012] WO 00/66589 deals with the synthesis and pharmaceutical use of Epothilone derivatives having an alkenyl-, alkynyl-, or an cyclic ether containing substituent at the 6-position of the macrocyclic ring.

[0013] WO 00/49021 discloses Epothilone derivatives with a halogen substituent in 16-position and their synthesis.

[0014] WO 00/71521 discloses a method for the synthesis of olefinic Epothilones.

[0015] WO 98/25929 deals with the manufacture of libraries of Epothilone analogs.

[0016] WO 99/43320 mentions, in a very general manner, the use of Epothilones for the treatment of cancer. The disclosure focuses on the development of application conditions for the particular compound Epothilone B for the treatment of a wide range of cancer varieties. There is no mention in this document of the difficulties of treating brain diseases associated with proliferative processes as discussed above, or of any specific advantages of using Epothilones in this regard.

[0017] It has now unexpectedly been found that certain Epothilones show a particularly good ability to penetrate the BBB compared to other cytostatic agents (antimitotic agents and others), and thus, are particularly useful for the manufacture of medicaments for the treatment of brain diseases associated with proliferative processes. Due to their pharmacological mechanism of action, these compounds can also be used for the treatment of diseases other than cancer, which are associated with proliferative activity.

20 Summary of the Invention

[0018] Accordingly, the present invention relates to the use of Epothilones for the treatment of brain diseases associated with proliferative processes, or for the preparation of a medicament for the treatment of brain diseases associated with proliferative processes. It also relates to methods of treating brain diseases associated with proliferative processes by oral, rectal, local, or parenteral, preferably inhalational, intravenous, or intraperitoneal, most preferably intravenous administration of an Epothilone.

[0019] For the purposes of the present invention, an Epothilone is defined as a cyclic molecule with a 16-membered ring and variable substituents and pharmaceutical activity as a cytostatic agent that binds to tubulin (Asnes et al., *Anal. Biochem.* 1979, 98, 64-73; Job et al., *Cellular Pharmacol.* 1993, 1 (Suppl. I), S7-S10; Lichner et al., *PNAS* 2001, 98, 11743-11748). The preferred Epothilones for use according to the present invention furthermore show an average distribution coefficient between plasma and brain of 0.3 to 1.5 as measured by the mouse bolus injection assay, as described herein.

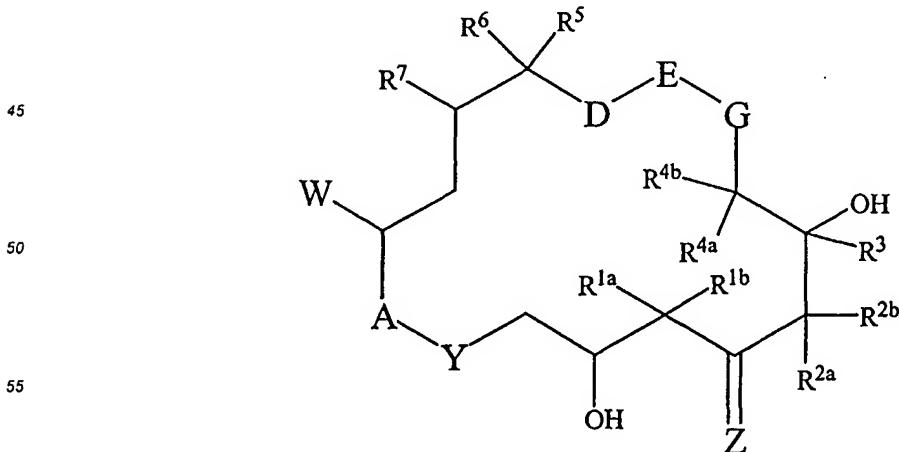
A further preferred subgroup is that wherein the Epothilone molecule is a lactone or a lactame molecule.

A preferred subgroup is that wherein the Epothilone shows an average distribution coefficient between plasma and brain of 0.6 to 1.2 in the mouse intravenous bolus injection assay.

A preferred subgroup is the use for the treatment of a brain disease selected from the group consisting of primary brain tumor, secondary brain tumor, Alzheimer's disease and multiple sclerosis.

[0020] Preferred Epothilones for use in the present invention are compounds of the general formula:

40



wherein:

5 R^{1a}, R^{1b} are each independently hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl, or together form a $-(CH_2)_m$ -group where m is 2 to 5;

10 R^{2a}, R^{2b} are each independently hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl, or together form a $-(CH_2)_n$ -group where n is 2 to 5, or C_2 - C_{10} alkenyl, or C_2 - C_{10} alkynyl;

15 R^3 is hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl;

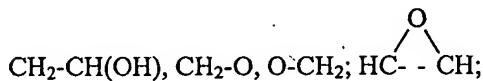
20 R^{4a}, R^{4b} are each independently hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl, or together form a $-(CH_2)_p$ - group where p is 2 to 5;

25 R^5 is hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl, CO_2H , CO_2 alkyl, CH_2OH , CH_2O alkyl, CH_2O acyl, CN , CH_2NH_2 , $CH_2N(alkyl, acyl)_{1,2}$, or CH_2Hal ;

30 R^6, R^7 are each hydrogen, or together form an additional bond, or together form an epoxy function;

35 G is O or CH_2 ;

40 D-E is a group H_2C-CH_2 , $HC=CH$, $C=C$, $CH(OH)-CH(OH)$, $CH(OH)-CH_2$,



50 W is a group $C(=X)R^8$, or is a bi- or tricyclic aromatic or heteroaromatic radical;

55 X is O , or two groups OR^{20} , or a C_2 - C_{10} alkylenedioxy group (which may be straight or branched), or H/OR^9 , or a group $CR^{10}R^{11}$;

60 R^8 is hydrogen, C_1 - C_{10} alkyl, aryl, aralkyl, halogen, CN ;

65 R^9 is hydrogen or a protecting group PG^x ;

70 R^{10}, R^{11} are each independently hydrogen, C_1 - C_{20} alkyl, aryl, aralkyl, or together with the methylene carbon form a 5- to 7-membered carbocyclic ring;

75 Z is O or H/OR^{12} ;

80 R^{12} is hydrogen or a protecting group PG^z ;

85 A-Y is a group $O-C(=O)$, $O-CH_2$, $CH_2-C(=O)$, $NR^{21}-C(=O)$, $NR^{21}-SO_2$;

90 R^{20} is a C_1 - C_{20} alkyl group;

95 R^{21} is hydrogen, or C_1 - C_{10} alkyl;

100 PG^x, PG^z is C_1 - C_{20} alkyl, C_4 - C_7 cycloalkyl, which may contain an oxygen atom in the ring, aryl, aralkyl, C_1 - C_{20} acyl, aroyl, C_1 - C_{20} alkylsulfonyl, arylsulfonyl, tri(C_1 - C_{20} alkyl)silyl, di(C_1 - C_{20} alkyl) arylsilyl, (C_1 - C_{20} alkyl)dialkylsilyl, or tri(aralkyl)silyl;

105 as a single stereoisomer or a mixture of different stereoisomers, and / or as a pharmaceutically acceptable salt thereof.

110 [0021] These compounds are advantageously used in the treatment of, or for the manufacture of a medicament for the treatment of, a brain disease associated with proliferative processes.

115 [0022] In a further embodiment, the present invention relates to a method of treating a brain disease associated with proliferative processes comprising administering to an individual in need thereof a therapeutically effective amount of

an Epothilone as defined above.

Preferred Embodiments

5 [0023] The term "brain disease associated with proliferative processes" as referred to in the context of the present invention includes, but is not limited to, primary brain tumors such as astrocytomas, oligodendrogiomas, pinealomas, medulloblastomas, neurilemmomas, meningiomas, and ependymomas, secondary brain tumors, multiple sclerosis, and Alzheimer's disease, all of which represent preferred brain diseases associated with proliferative processes to be treated in accordance with the present invention.

10 [0024] Particularly preferred brain diseases associated with proliferative processes to be treated by Epothilone administration in accordance with the present invention are primary and secondary brain tumors.

15 [0025] The term "therapeutically effective amount" as used herein refers to that amount of a compound of the invention which, when administered to an individual in need thereof, is sufficient to effect treatment, as defined below, for brain diseases associated with proliferative processes. The amount which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease and its severity, and the age of the human to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

20 [0026] "Treating" or "treatment" as used herein refers to the treatment of a brain disease in an individual, which disease is associated with proliferative processes; and include:

25 (i) preventing the disease from recurring in an individual, in particular, when such individual is in need of further medicamentous treatment after a previous surgical or medicamentous therapy;
 (ii) inhibiting the disease, i.e., arresting its development; or
 (iii) relieving the disease, i.e., causing regression of the disease.

25 [0027] The term "alkyl" as used herein refers to straight or branched alkyl groups, e.g., methyl, ethyl, propyl, isopropyl, *n*-butyl, *t*-butyl, *n*-pentyl, neopentyl, heptyl, or decyl. Alkyl groups can be perfluorinated or substituted by one to five substituents selected from the group consisting of halogen, hydroxy, C₁-C₄ alkoxy, or C₆-C₁₂ aryl (which can be substituted by one to three halogen atoms).

30 [0028] The term "aryl" as used herein refers to an aromatic carbocyclic or heterocyclic moiety containing five to 14 ring atoms, e.g., phenyl, naphthyl, furyl, thieryl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, chinolyl, or thiazolyl. Aryl groups can be substituted by one or more substituents selected from the group consisting of halogen, hydroxy, alkoxy, -CO₂H, -CO₂Alkyl, -NH₂, -NO₂, -N₃, -CN, C₁-C₂₀ alkyl, C₁-C₂₀ acyl, or C₁-C₂₀ acyloxy. The heteroatoms can be oxidized, if this does not cause a loss of aromatic character, e.g., a pyridine moiety can be oxidized to give a pyridine N-oxide.

35 [0029] The term "aralkyl" as used herein refers to a group which can contain up to 14 atoms in the aryl ring (preferred five to ten) and one to eight carbon atoms in the alkyl chain (preferred one to four), e.g., benzyl, phenylethyl, naphthylmethyl, naphthylethyl, furylmethyl, thiényl, or pyridylpropyl. The rings can be substituted by one or more substituents selected from the group consisting of halogen, hydroxy, alkoxy, -CO₂H, -CO₂Alkyl, -NH₂, -NO₂, -N₃, -CN, C₁-C₂₀ alkyl, C₁-C₂₀ acyl, or C₁-C₂₀ acyloxy.

40 [0030] The protecting groups PG can be alkyl- and/or aryl-substituted silyl moieties, C₁-C₂₀ alkyl, C₄-C₇ cycloalkyl, which may contain an oxygen atom in the ring, aryl, aralkyl, C₁-C₂₀ acyl, aroyl, alkyl- or arylsulfonyl. Groups which can be easily removed from the molecule are preferred, e.g., methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydrofuranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, as well as alkylsulfonyl or arylsulfonyl. Preferred acyl groups are formyl, acetyl, propionyl, pivaloyl, butyryl, or benzoyl, which all can be substituted by one or more amino and/or hydroxy moieties.

45 [0031] A preferred group is compounds of the general formula as given above, wherein A-Y is O-C(=O); D-E is H₂C-CH₂; G is CH₂; Z is O; R^{1a}, R^{1b} are both C₁-C₁₀ alkyl or form together a -(CH₂)_p- group where p is 2 to 3; R^{2a}, R^{2b} are each independently hydrogen, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ alkyne; R³ is hydrogen; R^{4a}, R^{4b} are each independently hydrogen or C₁-C₁₀ alkyl; R⁵ is C₁-C₁₀ alkyl.

50 [0032] Another preferred group is compounds of the general formula as given above, wherein R^{2a}, R^{2b} are each independently hydrogen, C₂-C₁₀ alkenyl or C₂-C₁₀ alkyne; R⁶, R⁷ form an epoxy function or together form an additional bond; W is a 2-Methylbenzothiazol-5-yl radical or a 2-Methylbenzoxazol-5-yl radical or a Quinoline-7-yl radical.

55 [0033] Of this group, a preferred subgroup is compounds selected from the following:

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzoxazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzoxazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

5 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

10 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-9,13-dimethyl-5,5-(1,3-trimethyl-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-12,16-dimethyl-8,8-(1,3-trimethylen)-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

15 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

20 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(chinolin-2-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cy-25 clohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-aza-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione; and

30 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4-aza-17-oxabicyclo[4.1.0]heptadecane-5,9-dione.

35 [0034] Another preferred group of compounds has the general formula as given above, wherein R^{2a}, R^{2b} are each independently hydrogen, or C₁-C₁₀ alkyl; R⁶, R⁷ form an epoxy function, or form an additional bond; W is a group C (=X)R⁸; X is a group CR¹⁰R¹¹; R⁸ is hydrogen, halogen, C₁-C₁₀ alkyl; R¹⁰, R¹¹ are hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl.

36 [0035] Of this group, a preferred subgroup is compounds selected from the following:

40 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

45 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

50 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-12,16-dimethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;

55 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-penta-

(4S,7R,8S,9S, 13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;

5 (1 S/R,3 S(E),7S, 10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethyl-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione;

10 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethyl-10,12,16-dimethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

15 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

20 (4S,7R,8S,9S, 13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione; and

(1S/R,3 S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione.

25 [0036] Another preferred group is compounds of the general formula as given above, wherein R^{2a}, R^{2b} are each independently hydrogen, C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl; R⁶, R⁷ form an epoxy function or together form an additional bond; W is a group C(=X)R⁸; X is a group CR¹⁰R¹¹; R⁸ is hydrogen, halogen, C₁-C₁₀ alkyl; R¹⁰, R¹¹ are hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl.

30 [0037] Of this group, a preferred subgroup is compounds selected from the following:

(4S,7R,8S,9S, 13E/Z, 16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-in-1-yl)-cyclohexadec-13-ene-2,6-dione;

35 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-in-1-yl)-3-(2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(4S,7R, 8S,9S,13 E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5, 5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2, 6-dione;

40 (1S/R,3 S(E),7S, 10R, 11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S, 13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(but-3-in-1-yl)-cyclohexadec-13-ene-2,6-dione;

45 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-in-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

50 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-en-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(1S/R,3S(E),7S,10R,11R, 12S,1 6R/S)-7, 11-dihydroxy-10-(but-3-en-1-yl)-3-(2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

55 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-in-1-yl)-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-in-1-yl)-3-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

nyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;

(4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione; and

(1S/R,3S(Z),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione.

[0038] The synthesis of the compounds listed above is described in the international patent applications WO 99/07692, WO 00/49021, and WO 00/66589, which are incorporated herein by reference.

[0039] For the use according to the invention, the compounds can be formulated by methods known in the art. Compositions for the oral, rectal, parenteral or local application can be prepared in the form of tablets, capsules, granulates, suppositories, implantates, sterile injectable aqueous or oily solutions, suspensions or emulsions, aerosols, salves, creams, or gels, retard preparations or retard implantates. The compounds may also be administered by implantable dosing systems.

[0040] The pharmaceutical active compound(s) can thus be mixed with adjuvants known in the art, such as gum arabic, talcum, starch, mannitol, methyl cellulose, lactose, surfactants such as tweens® or myrj®, magnesium stearate, aqueous or non-aqueous carriers, paraffin derivatives, wetting agents, dispersing agents, emulsifiers, preservatives, and flavors.

[0041] The compounds can be used in the form of their clathrates of α -, β -, or γ -cyclodextrin or of substituted α -, β -, or γ -cyclodextrines, or in the form of a liposomal composition, in particular a liposomal composition comprising a polyethyleneglycol(PEG)-derivatized lipid.

[0042] The invention also relates to pharmaceutical compositions containing one or more of the pharmaceutically active compounds listed above, and their use for the treatment and in the methods in accordance with the present invention. Preferably, one dose unit of these compositions contains about 0.01-100 mg of the pharmaceutically active compound(s). The dosage for the use according to the invention for a human is about 0.01-100 mg per day; a preferred dosage is about 0.02-70 mg per day; a more preferred dosage is about 0.04-40 mg per day.

Brief Description of the Figures

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[0043]

Figure 1 shows the plasma and brain concentrations of 4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-7-(1-propyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione (compound 1) after iv application, monitored over a period of 40 min, determined in the animal model of the Example.

Figure 2 shows the plasma and brain concentrations of 3 H-labeled dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione (compound 2) after iv application, monitored over a period of 40 min, determined in the animal model of the Example.

Figure 3 shows the plasma and brain concentrations of 3 H-labeled 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione (compound 3) after iv application, monitored over a period of 40 min, determined in the animal model of the Example.

Figure 4 shows the plasma and brain concentrations of 3 H-labeled paclitaxel after iv application, monitored over a period of 40 min, determined in the animal model of the Example.

Figure 5 shows the brain-plasma-ratio after iv application of the Epothilones of figures 1-3 and paclitaxel as comparison, monitored over a period of 40 minutes, derived from the data of figures 1-4.

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Example (Mouse bolus injection assay)

(*In vivo* assay for the evaluation of blood and brain levels of Epothilones)

[0044] Male SCID mice (20-25 g, non-leaky) were treated with a single dose of tritium-labeled Epothilones and paclitaxel (5 mg/kg; 7.4 MBq/mg; in 30 % Hydroxypropyl- β -cyclodextrin (HP β CD)/NaCl iv bolus injection). Partitioning of radioactivity between blood and brain was measured by liquid scintillation counting (LSC) and HPLC-radioflow at three time points (10, 20 and 40 min) after injection.

[0045] The following compounds were tested in this assay:

5 Paclitaxel;
compound 1: 4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-7-(1-propyl)-5,5,9,13-tetrame-thyl-cyclohexadec-13-ene-2,6-dione;
compound 2: dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-propyl-8,8,12,16-tetramethyl-4,17-diox-abicyclo[14.1.0]heptadecane-5,9-dione; and
compound 3: 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,17-diox-abicyclo[14.1.0]heptadecane-5,9-dione.

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Results:

15 [0046] All Epothilones were found in the brain at 40 min after iv application in concentrations that exceeded the plasma concentration. For compound 1 and 2 a higher brain plasma ratio was already observed after 20 min. For compound 3 at 10 and 20 minutes a high variation between the animals within one group was observed. 40 minutes after application paclitaxel was detected in the brain in considerable amounts, too.

20 [0047] When comparing the partial (0-40 min) areas under the plasma/brain level time curve, a ratio AUCbrain/AUC-plasma of approx. 1 was found (compound 1: 1.0; compound 2: 1.2; compound 3: 0.8) indicating a free access to the brain.

[0048] Paclitaxel was below the limit of quantitation in all brain samples but in comparable concentrations in plasma leading to a AUCbrain/AUCplasma ratio of zero.

[0049] Concentrations measured for these compounds and AUC ratios calculated thereof are summarized in table 1.

25 Conclusion:

[0050] In contrast to paclitaxel, Epothilones seem to penetrate the blood-brain-barrier to a significant extend. Per-sistence in the brain is longer compared to plasma.

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Table 1:

Compound (³ H-labeled)	Time (min)	Plasma conc. mean, (µg/ml)	Plasma (µg*min/ml) AUC (0-40min)	Brain conc. mean, (µg/g)	Brain (µg*min/ml) AUC (0-40min)	AUC Ratio Brain/Plasma
Compound 1	10	0,8		0,3		
	20	0,6	20	0,8	21	
	40	0,3		0,6		1,0
Compound 2	10	1,6		1,1		
	20	0,7	31	1,1	35	
	40	0,3		0,8		1,2
Compound 3	10	1,2		0,9		
	20	0,7	25	0,3	20	
	40	0,3		0,6		0,8
Paclitaxel	10	0,8		<LOQ		
	20	0,6	19	<LOQ	0	
	40	0,2		<LOQ		0,0

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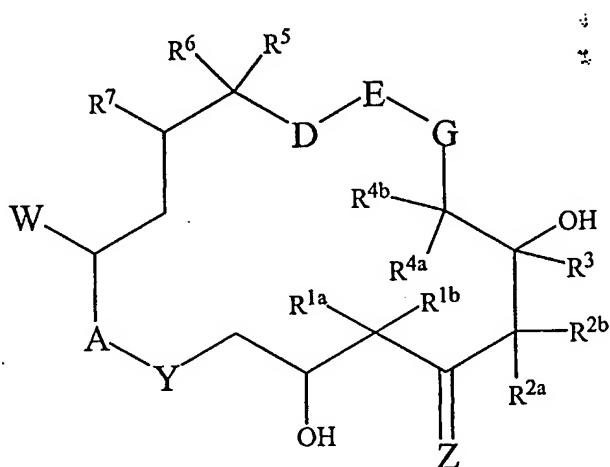
Claims

1. Use of an Epothilone, which shows an average distribution coefficient between plasma and brain of 0.3 to 1.5 in the mouse intravenous bolus injection assay, for the preparation of a medicament for the treatment of a brain disease associated with proliferative processes.

5 2. The use of claim 1, wherein the Epothilone is a lactone or a lactame molecule.

10 3. The use of claim 2, wherein the average distribution coefficient between plasma and brain is 0.6 to 1.2.

15 4. Use of a compound of the general formula:



wherein

35 R^{1a}, R^{1b} are each independently hydrogen, C₁-C₁₀ alkyl, aryl, aralkyl, or together form a -(CH₂)_m-group where m is 2 to 5;

40 R^{2a}, R^{2b} are each independently hydrogen, C₁-C₁₀ alkyl, aryl, aralkyl, or together form a -(CH₂)_n-group where n is 2 to 5, or C₂-C₁₀ alkenyl, or C₂-C₁₀ alkynyl;

45 R³ is hydrogen, C₁-C₁₀ alkyl, aryl, aralkyl;

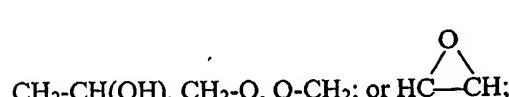
50 R^{4a}, R^{4b} are each independently hydrogen, C₁-C₁₀ alkyl, aryl, aralkyl, or together form a -(CH₂)_p-group where p is 2 to 5;

55 R⁵ is hydrogen, C₁-C₁₀ alkyl, aryl, aralkyl, CO₂H, CO₂alkyl, CH₂OH, CH₂Oalkyl, CH₂Oacyl, CN, CH₂NH₂, CH₂N(alkyl, acyl)_{1,2}, or CH₂Hal;

R⁶, R⁷ are each hydrogen, or together form an additional bond, or together form an epoxy function;

60 G is O or CH₂;

65 D-E is a group H₂C-CH₂, HC=CH, C≡C, CH(OH)-CH(OH), CH(OH)-CH₂,



W	is a group C(=X)R ⁸ , or is a bi- or tricyclic aromatic or heteroaromatic radical;
X	is O, or two groups OR ²⁰ , or a C ₂ -C ₁₀ alkylenedioxy group (which may be straight or branched), or H/OR ⁹ , or a group CR ¹⁰ R ¹¹ ;
5 R ⁸	is hydrogen, C ₁ -C ₁₀ alkyl, aryl, aralkyl, halogen, CN;
R ⁹	is hydrogen or a protecting group PG ^X ;
10 R ¹⁰ , R ¹¹	are each independently hydrogen, C ₁ -C ₂₀ alkyl, aryl, aralkyl, or together with the methylene carbon form a 5- to 7-membered carbocyclic ring;
Z	is O or H/OR ¹² ;
15 R ¹²	is hydrogen or a protecting group PG ^Z ;
A-Y	is a group O-C(=O), O-CH ₂ , CH ₂ -C(=O), NR ²¹ -C(=O), or NR ²¹ -SO ₂ ;
20 R ²⁰	is a C ₁ -C ₂₀ alkyl group;
25 R ²¹	is hydrogen, or C ₁ -C ₁₀ alkyl;
PG ^X , PG ^Z	is C ₁ -C ₂₀ alkyl, C ₄ -C ₇ cycloalkyl, which may contain an oxygen atom in the ring, aryl, aralkyl, C ₁ -C ₂₀ acyl, aroyl, C ₁ -C ₂₀ alkylsulfonyl, arylsulfonyl, tri(C ₁ -C ₂₀ alkyl)silyl, di(C ₁ -C ₂₀ alkyl) arylsilyl, (C ₁ -C ₂₀ alkyl) diarylsilyl, or tri(aralkyl)silyl;
30	as a single stereoisomer or a mixture of different stereoisomers, and / or as a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a brain disease associated with proliferative processes.
5. The use of any one of claims 1-4, where the brain disease is selected from the group consisting of primary brain tumor, secondary brain tumor, Alzheimer's disease and multiple sclerosis.	
35 6. The use of any one of claims 4 or 5, wherein	
A-Y	is O-C(=O);
D-E	is H ₂ C-CH ₂ ;
40 G	is CH ₂ ;
Z	is O;
45 R ^{1a} , R ^{1b}	are both C ₁ -C ₁₀ alkyl or together form a -(CH ₂) _m - group where m is 2 or 3;
R ^{2a} , R ^{2b}	are each independently hydrogen, C ₁ -C ₁₀ alkyl, C ₂ -C ₁₀ alkenyl, or C ₂ -C ₁₀ alkynyl;
R ³	is hydrogen;
50 R ^{4a} , R ^{4b}	are each independently hydrogen or C ₁ -C ₁₀ alkyl;
R ⁵	is C ₁ -C ₁₀ alkyl.
55 7. The use of any one of claims 4-6, wherein	
R ^{2a} , R ^{2b}	are each independently hydrogen, C ₂ -C ₁₀ alkenyl or C ₂ -C ₁₀ alkynyl;
R ⁶ , R ⁷	together form an epoxy function or an additional bond; and

W is a 2-Methylbenzothiazol-5-yl radical, a 2-Methylbenzoxazol-5-yl radical, or a Quinoline-7-yl radical.

8. The use of claim 7, wherein the compound is selected from the group consisting of:

5 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzoxazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

10 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzoxazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-9,13-dimethyl-5,5-(1,3-trimethylen)-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

25 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-12,16-dimethyl-8,8-(1,3-trimethylen)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;

35 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione; and

40 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(2-methyl-benzothiazol-5-yl)-1-aza-5,5,9,13-tetramethyl-7-(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-methyl-benzothiazol-5-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

9. The use of any one of claims 4-6, wherein

R^{2a}, R^{2b} are each independently hydrogen, or C₁-C₁₀ alkyl;

45 R⁶, R⁷ together form an epoxy function or an additional bond;

W is a group C(=X)R⁸;

X is a group CR¹⁰R¹¹;

50 R⁸ is hydrogen, halogen, or C₁-C₁₀ alkyl; and

R¹⁰, R¹¹ are hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl.

55 10. The use of claim 9, wherein the compound is selected from the group consisting of:

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

5 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,(1,3-trimethylen)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

10 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

15 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

20 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

25 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-12,16-dimethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

35 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-12,16-dimethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

40 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

45 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

50 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;

(1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-propyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

55 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-

7-propyl-cyclohexadec-13-ene-2,6-dione;
 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-9,13-dimethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;
 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-ethyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylen)-12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-S,S-(1,3-trimethylen)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione;
 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8-(1,3-trimethylen)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-propyl-cyclohexadec-13-ene-2,6-dione;
 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-propyl-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylen)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione;
 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylen)-10,12,16-dimethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione;
 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-chlor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-ethyl-cyclohexadec-13-ene-2,6-dione; and
 (1S/R,3S(Z),7S,10R,11S,12S,16R/S)-7,11-dihydroxy-3-(1-fluor-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-10-ethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

11. The use of any one of claims 4-6, wherein

R^{2a}, R^{2b} are each independently hydrogen, C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl;
 R⁶, R⁷ together form an epoxy function or an additional bond;
 W is a group C(=X)R⁸;
 X is a group CR¹⁰R¹¹;
 R⁸ is hydrogen, halogen, or C₁-C₁₀ alkyl; and
 R¹⁰, R¹¹ are hydrogen/2-methylthiazol-4-yl or hydrogen/2-pyridyl.

55 12. The use of claim 11, wherein the compound is selected from the group consisting of:

(4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-

7-(prop-2-in-1-yl)-cyclohexadec-13-ene-2,6-dione;
 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-in-1-yl)-3-(2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;
 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione;
 (1 S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;
 (4S,7R,8S,9S,13E/Z,16S(E))-4,8-dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(but-3-in-1-yl)-cyclohexadec-13-ene-2,6-dione;
 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-in-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;
 (1S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-en-1-yl)-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;
 (1 S/R,3S(E),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(but-3-en-1-yl)-3-(2-(2-pyridyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;
 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-in-1-yl)-cyclohexadec-13-ene-2,6-dione;
 (1S/R,3S(Z),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-in-1-yl)-3-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione;
 (4S,7R,8S,9S,13E/Z,16S(Z))-4,8-dihydroxy-16-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-7-(prop-2-en-1-yl)-cyclohexadec-13-ene-2,6-dione; and
 (1S/R,3S(Z),7S,10R,11R,12S,16R/S)-7,11-dihydroxy-10-(prop-2-en-1-yl)-3-(1-fluor-2-(2-methylthiazol-4-yl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[4.1.0]heptadecane-5,9-dione.

35 13. A method of treating a brain disease associated with proliferative processes comprising administering to an individual in need thereof a therapeutically effective amount of an Epothilone as defined in any one of claims 1 to 12.

40 14. The use or the method according to any one of claims 1 to 12, wherein the medicament or the Epothilone is to be administered orally, parenterally, rectally, or locally.

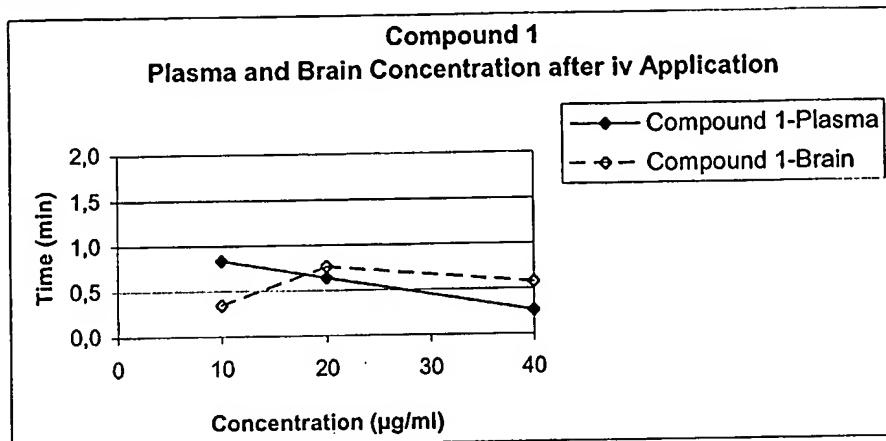
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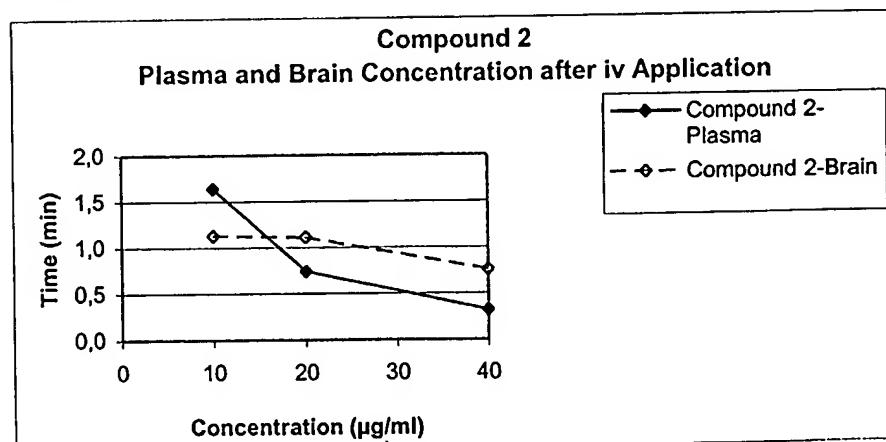
Figures

Figure 1:



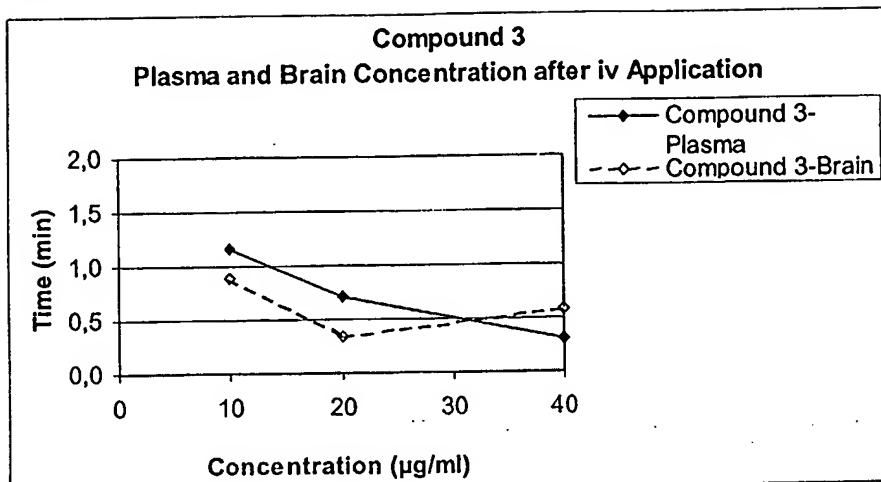
Compound 1: 4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-7-(1-propyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

Figure 2:



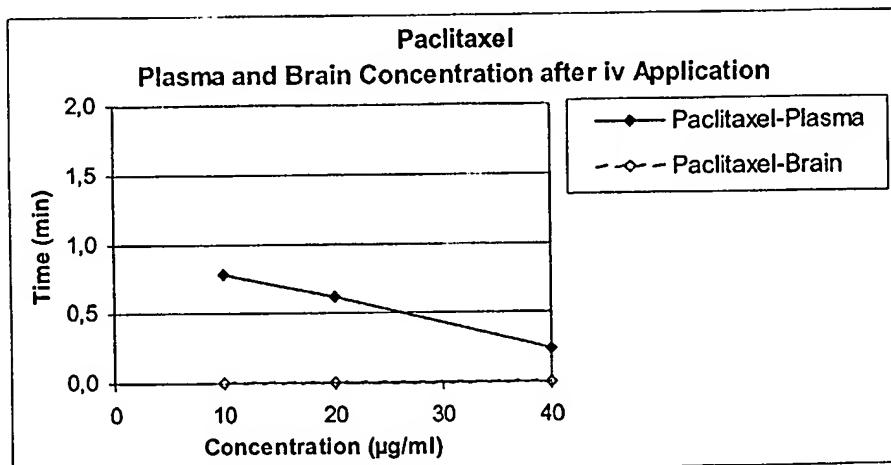
Compound 2: dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

Figure 3:

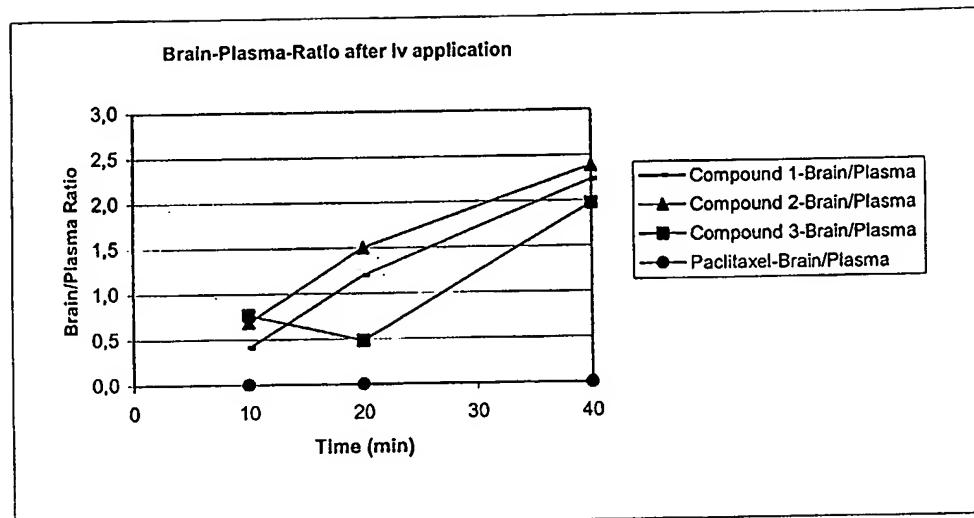


Compound 3: 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

Figure 4:



Compound: Paclitaxel

Figure 5:

Compound 1: 4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-1-oxa-7-(1-propyl)-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione;

Compound 2: dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)-ethenyl)-10-propyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

Compound 3: 7,11-dihydroxy-3-(2-methylbenzothiazol-5-yl)-10-(prop-2-en-1-yl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.



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PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 02 00 4745
shall be considered, for the purposes of subsequent
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	WO 01 92255 A (KOSAN BIOSCIENCES INC ;ASHLEY GARY (US); FARDIS MARIA (US); SANTI) 6 December 2001 (2001-12-06) * page 39, line 18-20 * * page 41, line 7 * * claims 17,18,21,22 *	1-7,9, 13,14	A61K31/428 A61K31/423 A61K31/4709 A61K31/427 A61K31/4427 A61P25/28 A61P35/00
Y	---	1-14	
X	WO 99 67253 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); NICOLAOU KYRIACOS) 29 December 1999 (1999-12-29) * page 3, paragraph 2 * * claims 1-8 *	1-6,9, 13,14	
Y	---	1-14	
X,D	WO 99 02514 A (SQUIBB BRISTOL MYERS CO) 21 January 1999 (1999-01-21) * page 9, line 21 - page 10, line 9 * * claims 1,2,4 *	1-6,9, 13,14	
Y	---	1-14 -/-	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			A61K A61P
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	15 August 2002	Bazzanini, R	
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : technological background O : non-written disclosure P : intermediate document</p> <p>& : member of the same patent family, corresponding document</p>	



Although claims 13 and 14 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Reason for the limitation of the search:

Present claims 1-6,7,9,11 relate to an extremely large number of possible compounds. Support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Moreover, present claims 1-14 relate to a compound defined (inter alia) by reference to the following parameter: "average distribution coefficient between plasma and brain".

The use of this parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC. It is impossible to compare the parameter the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Also, independent of the above reasoning, an attempt is made to define the compound by reference to its pharmacological profile (i.e. pharmacokinetics), rendering the scope of protection of said claims obscure (Art 84 EPC). It is pointed out that a compound cannot be sufficiently characterized by its pharmacokinetics. The use of such a functional definition is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature (e.g. compounds) to which it refers.

Furthermore, it could be understood that all the compounds falling under formulae of claims 4,6-12 possess the claimed "average distribution coefficient between plasma and brain", which seems to be essential for the treatment of the claimed brain diseases.

Consequently, the search concerning the compounds has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds listed in claims 8,10 and 12.

However some of the compounds listed in claim 8 (i.e. all the compounds of the series "dioxabicyclo") dont seem to correspond to the definition of substituent W given in claim 7 (see "(1-methyl-2" moiety before heterocyclic radical of "dioxabicyclo" compounds of claim 8). Therefore for the "dioxabicyclo" compounds the search has been performed taking into account the substituent W as described in claim 7.

Furthermore, present claims 1-4 relate to the treatment of a disease which actually is not well defined. The use of the definition "brain disease associated with proliferative process" in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC. It is impossible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a



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INCOMPLETE SEARCH
SHEET C

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meaningful complete search impossible. Consequently, the search concerning the therapeutic application of the claimed compounds has been restricted to the diseases listed in claim 5 and those reported in the description from page 8, line 27 to page 9, line 3.



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	WO 99 62510 A (ANGIOTECH PHARM INC ;HUNTER WILLIAM L (CA)) 9 December 1999 (1999-12-09) * claims 1,2,6,9,12 *	1-6,9, 13,14	
Y	---	1-14	
X	WO 01 24763 A (IMMUNOGEN INC ;CHARI RAVI V J (US)) 12 April 2001 (2001-04-12) * claims 1,2,18-20,31,32 *	1-6,9, 13,14	
Y	---	1-14	
X	LARNER A.J.: "Neuronal apoptosis as a therapeutic target in neurodegenerative disease." EXPERT OPINION ON THERAPEUTIC PATENTS, (2000) 10/10 (1493-1518). , XP000109764 * page 1508, left-hand column, line 2-10 * * page 1508, formulae 47, 48 *	1-6,13, 14	
Y	---	1-14	
Y,D	WO 00 66589 A (HOFFMANN JENS ;KLAR ULRICH (DE); BUCHMANN BERND (DE); SKUBALLA WERNE) 9 November 2000 (2000-11-09) * page 219, line 1-8 * * claims 1-21 * * page 246, line 20-22 *	1-14	
Y,D	WO 99 07692 A (KLAR ULRICH ;SCHERING AG (DE); BUCHMANN BERND (DE); SKUBALLA WERNE) 18 February 1999 (1999-02-18) * claims 1-8 * * page 165, line 6-11 *	1-14	
		-/-	

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Application Number

EP 02 00 4745

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
Y,D	WO 00 49021 A (KLAR ULRICH ;SCHERING AG (DE); BUCHMANN BERND (DE); SKUBALLA WERNE) 24 August 2000 (2000-08-24) * claims 1-55 * * page 94, line 13-20 * -----	1-14	
Y	NICOLAOU K C ET AL: "Chemical Biology of Epothilones" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 37, no. 15, August 1998 (1998-08), pages 2014-2045, XP002131418 ISSN: 0570-0833 * page 2037, left-hand column, paragraph 2 - page 2040, right-hand column, paragraph 3 * * tables 1-6 * * figure 10 * -----	1-14	

ANNEX TO THE EUROPEAN SEARCH REPORT
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This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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15-08-2002

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0192255	A	06-12-2001	AU 6658301 A WO 0192255 A2 US 2002045609 A1	11-12-2001 06-12-2001 18-04-2002
WO 9967253	A	29-12-1999	US 6380394 B1 AU 4774899 A AU 4775299 A BR 9911420 A CN 1306531 T WO 9967252 A2 WO 9967253 A2 EP 1089998 A2 HU 0102711 A2 JP 2002518504 T NO 20006378 A PL 345327 A1 SK 19712000 A3 TR 200003844 T2	30-04-2002 10-01-2000 10-01-2000 20-03-2001 01-08-2001 29-12-1999 29-12-1999 11-04-2001 28-12-2001 25-06-2002 21-02-2001 17-12-2001 11-09-2001 20-04-2001
WO 9902514	A	21-01-1999	AU 731497 B2 AU 7972098 A BG 104068 A BR 9810555 A CN 1270589 T EE 200000013 A EP 1019389 A2 JP 2002512634 T LT 99153 A ,B LV 12569 A LV 12569 B NO 200000076 A NZ 501198 A PL 338003 A1 SK 181799 A3 TR 200000065 T2 WO 9902514 A2 ZA 9805938 A	29-03-2001 08-02-1999 29-09-2000 15-08-2000 18-10-2000 15-08-2000 19-07-2000 23-04-2002 25-08-2000 20-11-2000 20-04-2001 07-01-2000 28-09-2001 25-09-2000 06-08-2001 21-11-2000 21-01-1999 10-01-2000
WO 9962510	A	09-12-1999	AU 4025599 A WO 9962510 A2 US 2002013298 A1	20-12-1999 09-12-1999 31-01-2002
WO 0124763	A	12-04-2001	AU 7988500 A EP 1229934 A2 WO 0124763 A2	10-05-2001 14-08-2002 12-04-2001

ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

EP 02 00 4745

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-08-2002

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0066589	A	09-11-2000	DE 19921086 A1 DE 10015836 A1 DE 19954228 A1 AU 4310300 A BG 106053 A BR 0010190 A CN 1349534 T CZ 20013885 A3 EP 1173441 A1 WO 0066589 A1 NO 20015278 A	02-11-2000 11-10-2001 13-09-2001 17-11-2000 31-05-2002 08-01-2002 15-05-2002 17-04-2002 23-01-2002 09-11-2000 21-12-2001
WO 9907692	A	18-02-1999	DE 19735574 A1 DE 19735575 A1 DE 19735578 A1 DE 19748928 A1 DE 19749717 A1 DE 19751200 A1 DE 19813821 A1 AU 9340998 A WO 9907692 A2 EP 1005465 A2 JP 2001512723 T ZA 9810403 A	11-02-1999 11-02-1999 11-02-1999 29-04-1999 06-05-1999 20-05-1999 23-09-1999 01-03-1999 18-02-1999 07-06-2000 28-08-2001 15-05-2000
WO 0049021	A	24-08-2000	DE 19908765 A1 DE 19954230 A1 AU 3156700 A BG 105802 A BR 0008331 A CN 1341115 T CZ 20012951 A3 WO 0049021 A2 EP 1150980 A2 NO 20014013 A	24-08-2000 15-11-2001 04-09-2000 29-03-2002 29-01-2002 20-03-2002 14-11-2001 24-08-2000 07-11-2001 18-10-2001

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82